Breast Cancer Prevention

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Dr. Trevor Powles’ review [1] of current results from clinical trials of agents that may prevent breast cancer from ever beginning or suppress preclinical disease touches on several issues critical in interpreting our understanding of this subject and on translating this understanding into evidence-based clinical practice. This commentary restates, emphasizes, and expands on the most important issues.

THE ABSENCE OF A COMPREHENSIVE MODEL OF BREAST CANCER DEVELOPMENT

While there is no doubt that estrogen plays a significant role in breast cancer development, we currently have no satisfying models that explain, well and completely, identified epidemiologic risk factors for this disease. Which hormones are most critical? What is the role of progestogens? When in women’s lives are hormonal effects on the breast most critical; in particular, how important are in utero and congenital hormonal exposures? Such questions emphasize some important aspects of hormonal “prevention:” complexity, effects of hormones over long periods of time, and the multiorgan system nature of the particular hormonal biology focused on here. Before addressing the broad clinical issues Powles’ data review raises, these biological uncertainties demand our consideration. Subject in point: the role of antiestrogen treatment in high-risk, presumed genetic-familial risk, women. Such women, BCRA1-presumptive or -proven carriers for example, have been considered a most important group to target for chemoprevention, and Powles correctly highlights our uncertainty about the results and role of tamoxifen in these women. On the one hand, clonic tumors from BCRA1 and BCRA2 mutation carriers are more likely to be hormone receptor-negative [2], and in an early analysis of small numbers of BCRA1 mutation carriers in the National Surgical Adjuvant Breast and Bowel Project breast cancer prevention trial, NSABP P-1, King has reported that tamoxifen was not associated with reduced numbers of breast cancers, while the opposite was true in BCRA2 mutation carriers [3].

These observations suggest that a hormonal treatment is not likely to prevent or suppress breast cancer in these BCRA1 women. On the other hand, Rebbeck found that prophylactic oophorectomy in BCRA1 mutation carriers was associated with decreased risk of later breast cancer [4]. One can argue that the absence of a testable model of breast cancer prevention is likely to make interpretation of clinical trials of prevention difficult, if not impossible.

THE NUMBERS GAME IN PREVENTION

The focus in breast cancer prevention trials has been on “high-risk” women for two broad reasons: to increase the numbers of events likely (i.e., cancers), and to increase the benefit:risk ratio. The general difficulty is that with the exception of laboratory-confirmed gene mutation carriers and women with lobular carcinoma in situ, other high-risk populations are small and have low absolute risks of developing breast cancer in the next 5-10 years [5,6]. Thus, in the larger broad “high-risk” trials Powles discusses, the intervention can, in the best of circumstances, benefit only a minority of women, while any side effects accrue to the entire treated group. Quantifying the short-term benefits is not as difficult as quantifying the spectrum of risks. This is particularly a challenge in trials where healthy volunteers participate, a circumstance that makes generalization of results to broader populations difficult.
WHICH BENEFITS AND RISKS ARE IMPORTANT IN BREAST CANCER PREVENTION?

Powles notes that the trials of tamoxifen and raloxifene reported to date have been concerned with breast cancer incidence data; and for NSABP P-1, the follow-up of cases has not continued after observation of a difference in this end point. These circumstances are important; subsequent reports of the NSABP P-1 trial have noted absence of cardiovascular benefits [7], but these data must be interpreted in light of the likely healthy volunteer population studied and the short-term treatment given and stopped when the breast cancer benefit was observed and communicated to the trial participants.

By far the most critical global issue here is the question of mortality benefit. Since the NSABP P-1 trial was stopped based on an incidence finding, we may never know if a mortality benefit would follow. In fact, the numbers and circumstances suggest that a mortality benefit is unlikely in the studied population. This is true for two reasons. First, the cancers suppressed by tamoxifen treatment were hormone receptor-positive lesions, which, had they not been suppressed, would have likely appeared and been diagnosed clinically as T₁ or T₂ at most, stage 1 (usually) cancers. Such clinical cancers are associated with an excellent prognosis [8]. Thus, mortality associated with the cancers likely to have been prevented would be small. Second, there are quantifiable incidence risk-“costs” of tamoxifen treatment. These are summarized in Table 1. These incident “events” can be associated with projections about lethality; pulmonary embolism, uterine malignancy, and stroke are each associated with some finite mortality rates. The rates of mortality here must be low but emphasize that mortality benefit from tamoxifen treatment of healthy women is far from certain (despite the dramatic breast cancer incidence benefit), particularly for postmenopausal women with a uterus.

A comprehensive analysis of the risks and benefits of tamoxifen in different patient groups in the NSABP P-1 trial [9] should be mandatory reading for clinicians considering use of tamoxifen in healthy women. This analysis essentially confirms the summarized picture in Table 1: in premenopausal women given low risks of major side effects, long-term benefit is more likely, while in postmenopausal women, the opposite is true.

Finally, with respect to benefits and risks, it must be emphasized that the data Powles reviews are of short-term treatment. The long-term consequences of a hormonal intervention, like tamoxifen, remain unknown and must be a concern. Over recent years we have seen clear evidence of the long-term consequences of oral contraceptive use; these observations should make us attentive to the possible multisystem consequences of tamoxifen or other breast cancer prevention interventions.

THE SYMPTOMATIC SIDE EFFECTS OF HORMONAL INTERVENTIONS IN BREAST CANCER PREVENTION

For women with life-threatening disease, symptomatic side effects that impair quality of life may be acceptable. For healthy women, the tolerance of such side effects must be predictably less. Tamoxifen is clearly associated with major increases in vasomotor symptoms [10]. These symptoms are likely the reason that perhaps one-quarter of women in prevention trials stop treatment. The analysis of risks and benefits of a prevention intervention for individual patients must consider those side effects also (Table 1).

| Table 1. Excess or prevented events if cohorts of 1,000 high-risk healthy women aged less than 50 years or aged 50 years or more with uteri are treated with tamoxifen for 5 years* |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| **Excess**      | <50 years       | ≥50 years       | **Prevented**   | <50 years       | ≥50 years       |
| Stroke          | —               | 4.7             | Breast cancer, invasive | 14.7            | 18.0            |
| Deep vein thrombosis | 1.5            | 3.2             | Breast cancer, noninvasive | 6.7             | 6.7             |
| Deep vein thrombosis with pulmonary embolism | 0.5 | 3.5 | Fractures | — | 7.6 |
| Cataracts       | —               | 15.5            | Subtotal        | 21.4            | 32.3            |
| Uterine cancer  | 1.2             | 11.5            |                 |                 |                 |
| Subtotal        | 3.2             | 38.4            |                 |                 |                 |
| Vasomotor symptoms\(^a\) | 170 | 170 |                 |                 |                 |
| Gynecologic symptoms\(^b\) | 160 | 160 |                 |                 |                 |

*Data from Fisher et al. [11] were used.

\(^a\)Hot flashes: “bothersome, quite a bit, and extremely.”

\(^b\)Vaginal discharge: “moderately, quite a bit, and extremely.”

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REFERENCES

1 Powles TJ. Breast cancer prevention. The Oncologist 2002;7:60-64.


